I. The § 112 Rejections

A. Rejection of claims 1-6, 8-13, 30-35, 34-42, 44, 46-50 under 35 U.S.C. § 112 ¶ 1.

The Examiner has maintained the rejection of claims 1-6, 8-13, 30-35, 34-42, 44 and 46-50 asserting that the specification, while being enabling for testosterone, its pharmaceutically acceptable salts, esters and amides, and testosterone derivatives as defined on page 15 of the specification, "does not reasonably provide enablement for analogs, all derivatives and prodrugs thereof." (Page 2, Paragraph 3). Applicant has therefore amended its claims to recite only testosterone, its pharmaceutically acceptable salts, esters and amides, and the testosterone derivatives defined on page 15 of the specification. Accordingly, Applicant respectfully requests reconsideration and withdrawal of this rejection under § 112 ¶ 1.

B. Rejection of claims 1-14, and 30-50 under 35 U.S.C. § 112 ¶ 1.

Applicant appreciates the Examiner's withdrawal of the rejection of claims 1-14 and 30-50 under § 112 ¶ 1 discussed in Paragraph 5 of the first office action.

C. Rejection of claims 1-7, 8-14 and 30-50 under 35 U.S.C. § 112 ¶ 2.

The Examiner has maintained the rejection of claims 1-7, 8-14 and 30-50 under § 112 ¶ 2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In view of the amendment to the claims, Applicant respectfully requests reconsideration and withdrawal of this rejection under § 112 ¶ 2.

D. Rejection of claim 2 under 35 U.S.C. § 112, ¶ 2.

Applicant appreciates the Examiner's withdrawal of the rejection of claim 2 under § 112 ¶ 2 for lack of antecedent basis as discussed in Paragraph 8 of the first office action.

E. Rejection of claims 2, 4, 5, 9, 11, 12, 31, 33, 34, 38, 40, 41, 46, 48 and 49 under 35 U.S.C. § 112 ¶ 2.

The Examiner has maintained the rejection of claims 2, 4, 5, 9, 11, 12, 31, 33, 34, 38, 40, 41, 46, 48 and 49 under 35 U.S.C. § 112 ¶ 2 as being indefinite for use of the term "includes." Applicant has amended the claims to remove the term "includes" and therefore respectfully requests reconsideration and withdrawal of this rejection under § 112 ¶ 2.

II. Summary of the Claims

The present invention is concerned with a method for controlling insulin resistance in diabetic humans. Insulin resistance is caused by elevated serum levels of insulin (hyperinsulinemia) or elevated tissue levels of glycogen and glucose. Hyperinsulinemia also depresses the normal production of anabolic steroids including testosterone, DHEA and growth hormone. Unlike hyperglycemia wherein the serum contains elevated levels of glucose, the addition of insulin does not correct hyperinsulinemia or decrease intracellular deposits of glucose or glycogen. The present invention therefore discloses a method for treating elevated serum levels of insulin and elevated tissue levels of glycogen and glucose. The present invention also discloses a method for lowering the hemoglobin A1C concentration in a human subject, a method for treating Syndrome X and a method for treating insulin resistance by calculating the ratio of the concentration of testosterone to the concentration of sex hormone binding globulin to determine the effective amount of testosterone to be administered to a human subject.

Independent claim 1, as amended, recites a method for controlling elevated tissue levels of glucose or glycogen. A human subject exhibiting elevated tissue levels of glucose or glycogen is first identified. Second, the subject is selected based upon a predetermined testosterone ratio test. Finally, a pharmacologically effective amount of testosterone or its pharmaceutically acceptable salts, esters and amides is administered to the human subject in order to control the elevated tissue levels of glucose or glycogen.

Independent claim 8 recites a method for treating elevated serum levels of insulin in a human subject. The method includes identifying a human subject exhibiting elevated serum levels of insulin and selecting the subject based upon a predetermined testosterone ratio test. The subject is then given a pharmacologically effective amount of testosterone or its pharmaceutically acceptable salts, esters and amides to control the elevated serum levels of insulin.

Independent claim 30 recites a method for lowering the hemoglobin A1C concentration in a subject by first identifying a human subject exhibiting abnormal hemoglobin A1C concentrations and selecting the subject based upon a predetermined testosterone ratio test. Next, the subject receives a pharmacologically effective amount of testosterone or its pharmaceutically acceptable salts, esters and amides to control the abnormal hemoglobin A1C concentration in the subject.

Independent claim 37 recites a method for treating Syndrome X in a subject. The first step involves identifying a human subject exhibiting Syndrome X then selecting the subject based upon a predetermined testosterone ratio test. Finally, a pharmacologically effective amount of testosterone or its pharmaceutically acceptable salts, esters and amides is administered to the subject to control the Syndrome X.

Lastly, independent claim 44 recites a method for treating insulin resistance in a subject by first obtaining a serum sample from a human subject. Next, the serum sample is assayed to determine both the concentration of total testosterone and the concentration of sex hormone binding globulin (SHBG) present in the sample. The ratio of the concentration of total testosterone to the concentration of SHBG in the sample is calculated and a pharmacologically effective amount of testosterone is administered to the subject if the ratio of the concentration of

total testosterone to the concentration of SHBG globulin in a male subject is less than approximately 0.5 and for a female subject is approximately 0.6 and greater.

III. The § 102(b) Rejections

A. Rejection of claims 1, 2, 8, 9, 30, 31, 37, 38, 44, and 46 over Coleman et al.

The Examiner has rejected claims 1, 2, 8, 9, 30, 31, 37, 38, 44, and 46 under 35 U.S.C. § 102(b) as being anticipated by the Coleman et al. reference (hereinafter "Coleman"). Coleman describes the effect of genetic background on the therapeutic effects of dehydroepiandrosterone (DHEA) in diabetes-obesity mutants and in aged normal mice. DHEA is an androgenic steroid, a metabolic product of the adrenal steroid hormones with about one-third of the androgenic activity of androsterone which is a metabolic product of testosterone. When fed to or injected in mice with inherited obesity-diabetes syndromes, DHEA acts as a potent anti-hyperglycemic and antidiabetic agent by improving glucose tolerance (hyperglycemia). As described by Coleman at page 27 in the first full paragraph, feeding DHEA to the genetically mutated diabetic mice restored the hyperglycemia of the mice to normal and improved glucose tolerance thereby converting the severe diabetes found in these mice to a well-compensated diabetes with severe obesity and insulin resistance.

Applicant respectfully submits that Coleman does not anticipate independent claims 1, 8, 30, 37, 44 and the claims depending therefrom because Coleman fails to include every element and limitation of these claims. Regarding claim 1, Coleman does not disclose treating elevated tissue levels of glucose and glycogen in a human subject by selecting a human subject based upon a predetermined testosterone ratio test which measures consistent hormonal changes in the subject. Nor does Coleman disclose the administration of testosterone or its pharmaceutically acceptable salts, esters and amides to a subject to control insulin resistance by

treating elevated tissue levels of glucose and glycogen. Rather, Coleman focuses solely on the use of DHEA to improve serum glucose tolerance (hyperglycemia) which is only one component of diabetes. No reference is made anywhere in Coleman to the effective administration of testosterone or the use of testosterone ratio tests to select subjects nor is DHEA used to treat insulin resistance in Coleman's mice. Instead, Coleman treats glucose tolerance through the administration of DHEA. Thus, Coleman's failure to disclose the use of testosterone to treat elevated tissue levels of glucose or glycogen cannot be read back into the reference by implication. See In re Evanega, 4 USPQ2d 1249 (Fed. Cir. 1987).

The Examiner states that an "ordinary artisan in the art at the time of the invention would know that tests done in mice can be extrapolated to human[s] and, thus, would know that the antihyperglycemic or antidiabetic effect shown by Coleman in mice would be applicable to human[s]." See Page 6, Paragraph 1. This argument is inapposite for two reasons. First, DHEA and testosterone are not interchangeable. While both DHEA and testosterone are androgenic steroids, DHEA is synthesized in the cortex of the adrenal gland not the testis as is testosterone. DHEA therefore exhibits significantly less androgenic activity than testosterone and cannot be interchanged therefor. Secondly, mice, unlike humans, possess very low natural levels of DHEA. It therefore does not follow that the effects of supra-physiological levels of DHEA in mice would be reproducible in humans. In fact, the literature has shown that DHEA therapy in humans with diabetes mellitus has no effect. See Exhibit A. This for the reason that serum levels of DHEA is independent of serum levels of insulin. See Exhibit B. Moreover, it has been indicated that "high doses of exogenous DHEA may produce adverse cardiovascular effects, an undesirable outcome in patients with diabetes mellitus." See Exhibit C. Treating hyperglycemia with DHEA therapy in order to increase serum levels of DHEA will not effect a decrease in serum insulin levels or intracellular glucose/glycogen levels. Coleman's DHEA therapy in mice

therefore cannot produce the same effects as the testosterone therapy of the present invention on insulin resistance in humans caused by elevated intracellular glucose/glycogen levels. Thus, Coleman does not anticipate Claim 1.

Similarly, Coleman fails to disclose all of the limitations of claim 8 including the treatment of elevated levels of insulin by selecting a subject through the use of a testosterone ratio test and administering a pharmacologically effective amount of testosterone or its pharmaceutically acceptable salts, esters and amides to the human subject. Claim 30 is also not anticipated by Coleman in that there is no reference whatsoever to the treatment of elevated hemoglobin A1C concentrations by the administration of testosterone nor the selection of subjects for such treatment through the use of testosterone ratio tests. Further, Coleman does not disclose the treatment of Syndrome X through the selection of a human subject exhibiting Syndrome X based upon a testosterone ratio test and administering a pharmacologically effective amount of testosterone to the human subject. For these reasons and the reasons discussed above in connection with Claim 1, Applicant respectfully submits that Claims 8, 30 and 37 are not anticipated by Coleman.

Finally, Coleman fails to disclose the limitations of Claim 44, namely, treating insulin resistance through assaying a serum sample to calculate the ratio of the concentration of total testosterone and the concentration of sex hormone binding globulin (SHBG) to administer a pharmacologically effective amount of testosterone to the subject if the ratio in a male subject is less than approximately 0.5 and for a female subject is approximately 0.06 and greater. There is no disclosure by Coleman of a method for determining the effective amount of hormonal replacement needed to offset insulin resistance in humans.

Because Coleman fails to disclose every limitation of independent claims 1, 8, 30, 37 and 44, it does not anticipate these claims and the claims depending therefrom and cannot therefore

cannot be used to support a rejection under § 102(b). Applicant therefore respectfully requests that the rejection be withdrawn.

B. Rejection of claims 1, 2, 8, 9, 30, 31, 37, 38, 44, and 46 over Moller et al. and Mauriello et al.

The Examiner has also rejected claims 1, 2, 8, 9, 30, 31, 37, 38, 44, and 46 under § 102(b) as being anticipated by the Moller et al. reference (hereinafter "Moller") and the Mauriello et al. reference (hereinafter "Mauriello"). Moller discloses the treatment of cardiovascular diseases by the administration of testosterone. Moller concludes that cardiovascular disease is caused by anaerobic metabolism resulting in impaired carbohydrate metabolism. (Page 18). Moller goes on to discuss that impaired carbohydrate metabolism is a result of decreased insulin activity which is also associated with a reduction in glucose tolerance. In support for his theories, Moller quotes other sources for the proposition that testosterone is effective in treating hyperglycemia. This for the reason that testosterone is effective in improving glucose tolerance and increasing sensitivity to insulin. Therefore, Moller indirectly discloses others' treatment of hyperglycemia through the administration of testosterone.

However, there is no disclosure of treating elevated levels of tissue glucose and glycogen in order to control insulin resistance in Moller. As discussed above, while hyperglycemia is one facet of diabetes, it is not the only cause and is not a factor in insulin resistance. Unlike hyperglycemia, hyperinsulinemia and elevated tissue levels of glucose and glycogen cannot be treated through the addition of insulin. Moreover, Moller fails to disclose the use of testosterone ratio tests to select insulin resistant subjects. This is one of the limitations of claims 1 and 8 rather than part of the preamble as stated in the Final Office Action at page 7. Claims 1 and 8 specifically require three elements: (1) the identification of subjects having elevated tissue levels of glucose or glycogen (claim 1) or elevated serum levels of insulin (claim 8); (2) the selection of

those subjects through testosterone ratio tests; and (3) treatment by the administration of pharmacologically effective amounts of testosterone. Moller provides no disclosure of these elements and only discloses the treatment of hyperglycemia rather than hyperinsulinemia and elevated tissue levels of glucose and glycogen which are the subject of claims 1 and 8.

Similarly, Moller fails to disclose the treatment of elevated hemoglobin A1C concentrations by the identification and selection of human subjects through the use of a testosterone ratio test followed by administration of testosterone as required by claim 30. Moller also does not disclose the treatment of Syndrome X through the selection of a human subject based upon a testosterone ratio test and administering a pharmacologically effective amount of testosterone to the human subject as required by claim 37. Finally, Moller fails to disclose treating insulin resistance through assaying a serum sample to calculate the ratio of the concentration of total testosterone and the concentration of sex hormone binding globulin (SHBG) to administer a pharmacologically effective amount of testosterone to the subject if the ratio in a male subject is less than approximately 0.5 and for a female subject is approximately 0.06 and greater as required by claim 44.

Because Moller fails to disclose every limitation of independent claims 1, 8, 30, 37 and 44, it does not anticipate these claims and the claims depending therefrom and cannot therefore cannot be used to support a rejection under § 102(b). Applicant therefore respectfully requests that the rejection be withdrawn.

Turning to the Mauriello et al. reference, Mauriello discloses the use of testosterone in the treatment of leg ulcers. In the Office Action, the basis for the § 102(b) rejection over Mauriello is that " . . . Mauriello et al. teach the drop in the need for oral hyperglycemics and/or insulin in diabetic patients using testosterone or testosterone propionate." (Page 7-8). The

Examiner then concludes that the method of use taught by Mauriello is encompassed by the claims of the present invention.

However, as discussed above in connection with Coleman and Moller, Mauriello does not disclose the treatment of hyperinsulinemia and elevated levels of glucose and glycogen through the administration of testosterone. Moreover, Mauriello does not disclose the selection of insulin resistant subjects through the use of testosterone ratio tests as recited in claims 1 and 8. Similarly, Mauriello fails to disclose the selection of subjects having elevated hemoglobin A1C concentrations based upon testosterone ratios tests followed by the administration of testosterone or its pharmaceutically acceptable salts, esters and amides to control the hemoglobin A1C concentration as required by claim 30. There is also no reference in Mauriello regarding the treatment of Syndrome X as claimed in claim 37 through the selection of a human subject exhibiting Syndrome X based upon a testosterone ratio test and administering a pharmacologically effective amount of testosterone to the human subject. Finally, Mauriello fails to disclose the limitations of claim 44 which include treating insulin resistance through assaying a serum sample to calculate the ratio of the concentration of total testosterone and the concentration of sex hormone binding globulin (SHBG) to administer a pharmacologically effective amount of testosterone to the subject if the ratio in a male subject is less than approximately 0.5 and for a female subject is approximately 0.06 and greater. Finally, there is no disclosure in Mauriello as to effective dosage, long term use or effective management of testosterone therapy on diabetic humans.

Because Mauriello fails to disclose every limitation of independent claims 1, 8, 30, 37 and 44, it does not anticipate these claims and the claims depending therefrom and cannot therefore cannot be used to support a rejection under § 102(b). Applicant therefore respectfully requests that the rejection be withdrawn.

IV. The § 103 Rejections

The Examiner also rejected claims 1-14 and 30-50 under 35 U.S.C. § 103(a) as being unpatentable over Coleman, Moller or Mauriello. For the following reasons, Applicant respectfully submits that the present invention is not obvious under 35 U.S.C. § 103(a) and requests reconsideration and withdrawal of the § 103(a) rejection.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With respect to objective evidence of nonobviousness, Applicant submits that the record supports the conclusion that there are long-felt but unsolved needs met by the present invention. The present invention is directed to the particular problem of providing a new and improved method of treating insulin resistance by administering testosterone or its pharmaceutically acceptable salts, esters and amides to control hyperinsulinemia, elevated levels of glucose or glycogen in the tissue, elevated hemoglobin A1C concentrations, and Syndrome X. Further, the present invention meets the existing need for an objective test to select subjects having insulin resistance, elevated A1C concentrations or Syndrome X for treatment using testosterone.

Coleman, Moller and Mauriello do not teach or suggest the claimed invention. As discussed above in connection with the § 102(b) rejection of Applicant's claims based upon these

references, there is no teaching or suggestion of administering testosterone to control elevated levels of insulin in serum or glucose or glycogen in tissue. Rather, as stated by the Examiner in the first office action, Coleman teaches that DHEA is "a potent antihyperglycemic and antidiabetic agent" and Moller and Mauriello "teach the drop in the need for oral hypoglycemics and/or insulin in diabetic patients using testosterone or testosterone propionate." (Page 8, Paragraph 14). Medical experience, however, has demonstrated that the reduction of serum glucose corrects ketoacidosis but does not prevent other aspects of diabetes. See *Travers and Sayers*, 1970. Effective treatment for diabetes relies on correction of both hyperinsulinemia and high concentrations of cellular glucose and glycogen. The claimed invention is therefore directed toward a pharmacologic treatment for hyperinsulinemia and elevated cellular glucose or glycogen concentrations by detection of consistent changes in hormonal parameters. None of the cited references teach or suggest a treatment for hyperinsulinemia and increased concentration of cellular glucose and glycogen at all. Moreover, none of the cited references teach or suggest treatment for any aspect of diabetes involving (1) pre-selection of subjects based on the testosterone ratio test, (2) a testosterone dosing schedule, based on reaching specific serum concentration of testosterone, and (3) reversal of all three components of insulin resistance including hyperglycemia, hyperinsulinemia, and abnormal glycosylated hemoglobin A1C levels. The prior art merely teaches that testosterone or other androgenic steroids may be used to decrease insulin resistance through an increase in glucose tolerance.

In fact, Coleman teaches away from the present invention. While Coleman's DHEA treatment of diabetes in genetically mutated mice resulted in conversion of severe diabetes to a well-compensated diabetes, it did not change the insulin resistance of the affected mice. (See page 27, first full paragraph). Moller also teaches away from the use of testosterone to treat elevated levels of insulin when he states "experience shows that diabetic patients easily succumb

to insulin shock when treated with testosterone." This for the reason that while testosterone may help to lower blood glucose levels, a backlash may occur wherein the blood glucose levels are lowered too far and the hyperglycemic subjects may experience hypoglycemia instead. This is the opposite effect of the claimed invention which utilizes testosterone to decrease elevated levels of serum insulin.

In support of the § 103 rejection, the Examiner also asserts in the Final Office Action at pages 8-9 that "the prior art teaches testosterone lowers insulin resistance (i.e., increases sensitivity to insulin) and, thus, it would follow that there would be a decrease in hemoglobin A1C in patients given testosterone." However, the prior art does not teach or suggest the use of a testosterone ratio test to determine the pharmacologically effective amount of testosterone needed to decrease the level of hemoglobin A1C as required by amended claim 30.

The Examiner also concludes that a compound that lowers insulin resistance and is antihyperglycemic would be useful in treating Syndrome X because glucose intolerance, insulin resistance, increased LDL and decreased HDL are associated with Syndrome X and non-insulin dependent diabetes. (Page 9). However, it does not follow that the claimed invention which treats different components of the Syndrome X constellation is thereby rendered obvious. Treating hyperglycemia does not affect the onset of hyperinsulinemia or elevated cellular concentration of glycogen. Moreover, there is no teaching or suggestion in any of the cited references that testosterone is effective in treating these components of Syndrome X which can exist independently of hyperglycemia. There is also no teaching or suggestion in Coleman, Moller or Mauriello to identify Syndrome X sufferers by testing for consistent hormonal changes through the use of a testosterone ratio test as required by claim 37.

Furthermore, none of the references disclose any suggestion whatsoever to treat insulin resistance by calculating the ratio of the concentration of total testosterone to the concentration

of SHBG in a serum sample in order to determine the pharmacologically effective amount of testosterone necessary to treat a subject with insulin resistance if the ratio in men is less than 0.5 and the ratio in women is greater than 0.06. Neither the first office action nor the final office action provide a basis for rejecting these limitations as shown in claim 44 under § 103.

Finally, prima facie obviousness requires that there must be a reasonable expectation of success when prior art is modified or combined. In the present application, there is no reasonable expectation of success in achieving the invention as claimed when the cited references are modified or combined. As discussed above, none of the cited references contain all the elements of Applicants' independent claims 1, 8, 30, 37 and 44. Unless all the elements are taught by the references, there can be no success in modifying them.

Thus, at the time the present invention was made, none of the references cited by the Examiner teach or describe *all* of the limitations claimed by Applicant in independent claims 1, 8, 30, 37 and 44 and the claims depending therefrom. It would therefore not have been obvious to one of ordinary skill in the art to provide a method for treating hyperinsulinemia, elevated cellular glycogen or glucose concentrations, elevated hemoglobin A1C concentrations, and Syndrome X wherein appropriate subjects for treatment are determined through testosterone ratio tests. Accordingly, independent claims 1, 8, 30, 37 and 44 and the claims depending therefrom are nonobvious under § 103 (a).

V. Conclusion

The applicant respectfully requests withdrawal of the rejections and believes that the claims as presented represent allowable subject matter. However, if the Examiner desires, the applicant is ready for a telephone interview to expedite prosecution. As always, the Examiner is

free to call the undersigned at 312-876-2622. The Examiner's attention is also drawn to the proper correspondence address shown below.

Respectfully submitted,
By its attorney,

Shashank Upadhye, Reg. No. 48,209

Date: 12 April, 2002

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN CLAIMS

Claims 1-14 and 30-50 have been amended as follows:

1. (Twice Amended) A method for controlling [serum-glucose] elevated tissue glucose or glycogen levels in a subject[, said method] comprising the steps of:

(a) identifying a human subject exhibiting [abnormal insulin resistance] elevated tissue glucose or glycogen levels;

(b) selecting the subject based on a predetermined testosterone ratio test; and

(c) administering a pharmacologically effective amount of testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject to control the [abnormal insulin resistance] elevated tissue glucose or glycogen levels.

2. (Twice Amended) The method according to claim 1, wherein the step of administering [includes] further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by intramuscular administration.

3. (Twice Amended) The method according to claim 1, wherein the step of administering further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by subcutaneous administration.

4. (Amended) [A] The method according to claim 1, wherein the step of administering [includes] further comprises disposing a pellet containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] into the subject.

5. (Amended) [A] The method according to claim 1, wherein [said] the step of administering [step includes] further comprises applying a transdermal gel containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof, in]to the subject.

6. (Twice Amended) The method according to claim 1, wherein the dosage of the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] ranges from approximately 15 mg to 40 mg per day.

7. (Amended) [A] The method according to claim 1, wherein [said] the testosterone [derivative comprises] is selected from the group consisting of testosterone enanthate, testosterone proprionate, testosterone cyprionate, nandrolone phenproprionate and decanoate, methyl-testosterone, fluoxymesterone, oxymetholone, methandrostenolone methandriol, norethandrolone, stanozol, dihydrotestosterone and combinations thereof.

8. (Twice Amended) A method for treating [insulin resistance] elevated serum levels of insulin in a subject [having insulin resistance, said method] comprising the steps of:

(a) identifying a human subject exhibiting [abnormal insulin resistance[elevated serum levels of insulin;

(b) selecting the subject based on a predetermined testosterone ratio test; and

(c) administering a pharmacologically effective amount of the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,]to the subject to control the elevated serum levels of insulin [resistance].

9. (Twice Amended) [A] The method according to claim 8, wherein the step of administering [includes] further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by intramuscular administration.

10. (Twice Amended) [A] The method according to claim 8, wherein the step of administering further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by subcutaneous administration.

11. (Amended) [A] The method according to claim 8., wherein [said] the step of administering [step includes] further comprises disposing a pellet containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] into the subject.

12. (Amended) [A] The method according to claim 8, wherein [said] the step of administering [step includes] further comprises applying a transdermal gel containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject.

13. (Amended) [A] The method according to claim 8, wherein the dosage of the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] ranges from approximately 15 mg to 40 mg[/] per day.

14. (Amended) [A] The method according to claim 8, wherein [said] the testosterone [derivative comprises] is selected from the group consisting of testosterone enanthate, testosterone proprionate, testosterone cyprionate, nandrolone phenproprionate and decanoate, methyl-testosterone, fluoxymesterone, oxymetholone, methandrostenolone methandriol, norethandrolone, stanozol, dihydrotestosterone, and combinations thereof.

30. (Twice Amended) A method for lowering the hemoglobin A1C concentration in a subject[, said method] comprising the steps of:

(a) identifying a human subject exhibiting abnormal hemoglobin A1C concentrations;

(b) selecting the subject based on a predetermined testosterone ratio test; and

(c) administering a pharmacologically effective amount of testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to control the abnormal hemoglobin A1C concentration in the subject.

31. (Twice Amended) The method according to claim 30, wherein the step of administering [includes] further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by intramuscular administration.

32. (Twice Amended) The method according to claim 30, wherein the step of administering [includes] further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by subcutaneous administration.

33. (Amended) [A] The method according to claim 30, wherein [said] the step of administering [step includes] further comprises disposing a pellet containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] into the subject.

34. (Amended) [A] The method according to claim 30, wherein [said] the step of administering [step includes] further comprises applying a transdermal gel containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof, in]to the subject.

35. (Twice Amended) The method according to claim 30, wherein the dosage of the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] ranges from approximately 15 mg to 40 mg per day.

36. (Amended) [A] The method according to claim 30 wherein [said] the testosterone [derivative comprises] is selected from the group consisting of testosterone enanthate, testosterone proprionate, testosterone cyprionate, nandrolone phenproprionate and decanoate, methyl-testosterone, fluoxymesterone, oxymetholone, methandrostenolone methandriol, norethandrolone, stanozol, dihydrotestosterone, and combinations thereof.

37. (Twice Amended) A method for treating Syndrome X in a subject [having Syndrome X, said method] comprising the steps of:

(a) identifying a human subject exhibiting Syndrome X;

(b) selecting the subject based on a predetermined testosterone ratio test; and

(c) administering a pharmacologically effective amount of testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject to control the Syndrome X.

38. (Twice Amended) [A] The method according to claim 37, wherein the step of administering [includes] further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by intramuscular administration.

39. (Twice Amended) [A] The method according to claim 37, wherein the step of administering further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by subcutaneous administration.

40. (Amended) [A] The method according to claim 37, wherein [said] the step of administering [step includes] further comprises disposing a pellet containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] into the subject.

41. (Amended) [A] The method according to claim 37, wherein [said] the step of administering [step includes] further comprises applying a transdermal gel containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject.

42. (Twice Amended) [A] The method according to claim 37, wherein the dosage of the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] ranges from approximately 15 mg to 40 mg per day.

43. (Amended) [A] The method according to claim 37, wherein [said] the testosterone [derivative comprises] is selected from the group consisting of testosterone enanthate, testosterone proprionate, testosterone cyprionate, nandrolone phenproprionate and decanoate, methyl-testosterone, fluoxymesterone, oxymetholone, methandrostenolone methandriol, norethandrolone, stanozol, dihydrotestosterone, and combinations thereof.

44. (Twice Amended) A method for treating insulin resistance in a subject [having insulin resistance, said method] comprising the steps of:

(a) obtaining a serum sample from a human subject;

(b) assaying the serum sample to determine both the concentration of total testosterone and the concentration of sex hormone binding globulin (SHBG) present in the sample;

(c) calculating the ratio of the concentration of total testosterone to the concentration of SHBG in the sample; and

(d) administering a pharmacologically effective amount of testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs

thereof,] to the subject if the ratio of the concentration of total testosterone to the concentration of SHBG globulin in a male subject is less than approximately 0.5 and for a female subject is approximately 0.06 and greater.

45. (Amended) The method according to claim 44, wherein the testosterone [derivative comprises] is selected from the group consisting of testosterone enanthate, testosterone proprionate, testosterone cyprionate, nandrolone phenproprionate and decanoate, methyl-testosterone, fluoxymesterone, oxymetholone, methandrostenolone methandriol, norethandrolone, stanozol, dihydrotestosterone, and combinations thereof.

46. (Twice Amended) The method according to claim 44, wherein the step of administering [includes] further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by intramuscular administration.

47. (Twice Amended) The method according to claim 44, wherein the step of administering further comprises administering the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] to the subject by subcutaneous administration.

48. (Amended) [A] The method according to claim 44, wherein [said] the step of administering [step includes] further comprises disposing a pellet containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] into the subject.

49. (Amended) [A] The method according to claim 44, wherein [said] the step of administering [step includes] further comprises applying a transdermal gel containing the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] [in]to the subject.

50. (Twice Amended) The method according to claim 44, wherein the dosage of the testosterone or [the analogs, derivatives, and] its pharmaceutically acceptable salts, esters[,] and amides[, and prodrugs thereof,] ranges from approximately 15 mg to 40 mg per day.